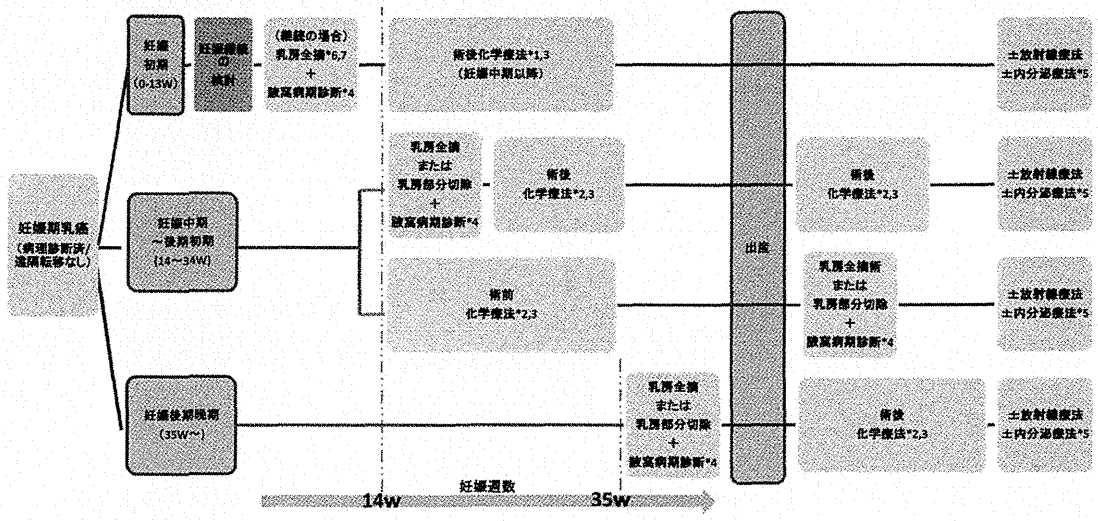


*1 化学療法は妊娠初期には施行すべきではなく，中期以降に施行すべきである．
*2 中期以降の化学療法施行時，出産予定に合わせ産科・乳腺治療医が相談し休薬・再開時期を慎重に検討すべきである．また化学療法施行に伴い，週数に比して成長がやや遅れる可能性も検討すべきである．
*3 妊娠中施行する化学療法では，CAF6サイクルがもっとも経験されているレジメンである．Taxianeについてはまだ安全性についてのデータが不十分である．またトラスツマブは禁忌である．
*4 妊娠中の腋窩病期診断でセンチネルリンパ節生検を施行する場合，色素法は禁忌であり，RI法単独が勧められる．
*5 放射線療法・内分泌療法は妊娠中は行われるべきではない．
*6 放射線療法を出産後まで待てない場合，乳房全摘が適応となる．
*7 妊娠初期の手術については妊娠週数に応じて麻酔科・産科と相談の上可否を検討するべきである．

図3 妊娠期乳癌の治療の流れ
（NCCN Guideline ver3.2012 Breast Cancer During Pregnancy より一部改変）

中止，また産後すぐには治療再開できないことから，出産前後の化学療法投与間隔が開くことが予想される．

（3）Late 3rd trimester（35週以降）

出産直前の化学療法は血液凝固系合併症の懸念があることから，この時期では手術が選択される．妊娠晩期での全身麻酔に伴う早産のリスクを念頭にいれ，産科・小児科・麻酔科の協力のもと準備して臨む必要がある．

いずれも出産後は通常乳癌と同様に集学的治療を行うことが重要である．産後の化学療法では，母乳への薬物移行の問題，部分切除症例では患側の乳腺炎のリスク，腋窩隔清症例では上肢浮腫に伴う蜂窩織炎のリスク，新生児を抱えての治療による精神負荷の増大などさまざまな問題を念頭に置き，多職種で対応できる体制を組む必要がある．

## 2．乳癌罹患患者の妊娠 —サバイバーの挙児希望—

### 1）乳癌罹患後の妊娠出産のリスクについて

かつては妊娠が乳癌の予後に及ぼす影響の恐れや過去の治療による卵子への影響の懸念から，乳癌罹患後の妊娠出産は避けられていた．しかし近年では多くの後方視的臨床研究から，ホルモン陽性乳癌を含め乳癌罹患患者の妊娠出産は乳癌の予後に影響しないという考え方が浸透しつつあり，今後サバイバーの妊娠出産に関する需要は高まると考えられる[32~34]．今までは妊孕性保護について議論されることは少なかったが，近年欧米では生殖年齢で薬物療法を施行されるすべての癌患者にとって検討されるべ

きという認識が広がり指針が示されている[35~37]．国内では乳癌専門医へのアンケート調査により乳腺治療医の知識と妊孕性保護への積極的姿勢が情報提供行動と関連することが示唆されており，治療医により患者の持つ情報や選択肢に差があることが推察されている[38]．今後患者の需要が多様化するなかで，私たち癌治療医と生殖医療専門家・産婦人科医の相互理解と協力体制の構築が急務であると考えている．

**2）化学療法や内分泌療法に伴う卵巣機能障害**

閉経前の乳癌患者に化学療法を施行したとき，多くの場合2～3カ月後に治療関連性無月経が認められる．治療終了後の月経再開は年齢が40歳以上で困難であると考えられているが，筆者らの検討では年齢に加え，化学療法の治療期間と化学療法後の内分泌療法施行の有無も月経再開の有無に関連することが示唆された[39~41]．一方，内分泌療法施行例ではタモキシフェンの催奇性による5年間の避妊が必要である．治療開始前に治療終了後の自然妊娠の可能性を予測することは理想であるが，現段階では困難である．一方で生殖医療の現場では卵巣機能は年齢に必ずしも相関しないと考えられており，将来の出産を希望している患者にとって，乳癌薬物療法は年齢に寄らずライフプランの変更を余儀なくされる可能性を含んでいるという認識が重要であり[5]，これらをあらかじめ患者に説明しメリット・デメリットを検討し治療方針を決定しなくてはならないと考えている．

**3）乳癌治療医と生殖医療専門医による支援システム —Oncofertilityとは—**

ここでは将来癌を克服して妊娠出産を望む患者に現段階で考えられる選択肢について述べる．治療終了後の自然妊娠の可能性を完全に予測することはできないが，治療開始前からARTのサポートを得ておくことで妊娠出産の可能性を広げることができる．具体的には薬物療法開始前に採卵し受精卵，未受精卵あるいは卵巣組織を凍結保存しておき，治療が落ち着いたら人工授精により妊娠するという方法である．この方法を選択するためには，治療開始前に乳癌の臨床病期や病理学的因子による再発リスク，薬物療法によるrisk reduction benefitとそのスケジュール，乳癌薬物療法開始前の卵巣機能および妊孕性の評価と予測される治療終了後の卵巣機能について，十分なアセスメントと情報提供が必要である．また患者の社会心理学的背景（パートナーの有無・家庭環境・経済的な問題）など条件も，重要な因子と考えられる．生殖医療を乳癌初回治療に組み込んだ場合，筆者らが考えている治療の流れを示す（**図4**）．

妊孕性保持支援において，乳癌治療医と生殖医療専門医の円滑な連携が必要と考えられたため，筆者らは日本生殖医学会に協力を依頼し生殖医療専門医に対し乳癌患者の生殖補助医療についての意識・行動についてのアンケート調査を行った．その結果排卵誘発剤を用いた場合の乳癌の予後への影響についてデータが数少ないことが問題としてあがったが，採卵や生殖補助を行うことは可能であるという見解を得た．また，乳癌治療医と生殖医療医の一定のコンセンサスや，施設間のネットワークの構築，施設内の支援体制の整備が必要であるという意見も多くあがった．日本生殖医学会のホームページには，本アンケート調査に基づいて筆者らが作成した乳癌患者の生殖補助医療への協力に賛同した医療機関の一覧が掲載されている[42]．

## おわりに

患者を理解し癌治療医として治療を練ることはもっとも重要であるが容易なことではない．とくに個々の妊娠と乳癌の問題を検討するためには患者の価値観・人生観の問題でもあることから，方針の決定には相応の時間が必要となる．現在筆者らの研究班では乳癌患者の将来の妊娠出産についてのポイントをまとめた患者向け情報提供リーフレットと，癌治療医や生殖専門医向けのガイドラインの作成に向け活動している．リーフレットやガイドラインにより癌治療医から患者への情報提供が簡便になり，日常臨床で取り入れやすくなるのではないかと考える．また妊娠期乳癌や乳癌罹患後の妊娠についてまだ不明な点が多く，それらを解決するためにはこの2つについてのデータベース構築も重要であると考え

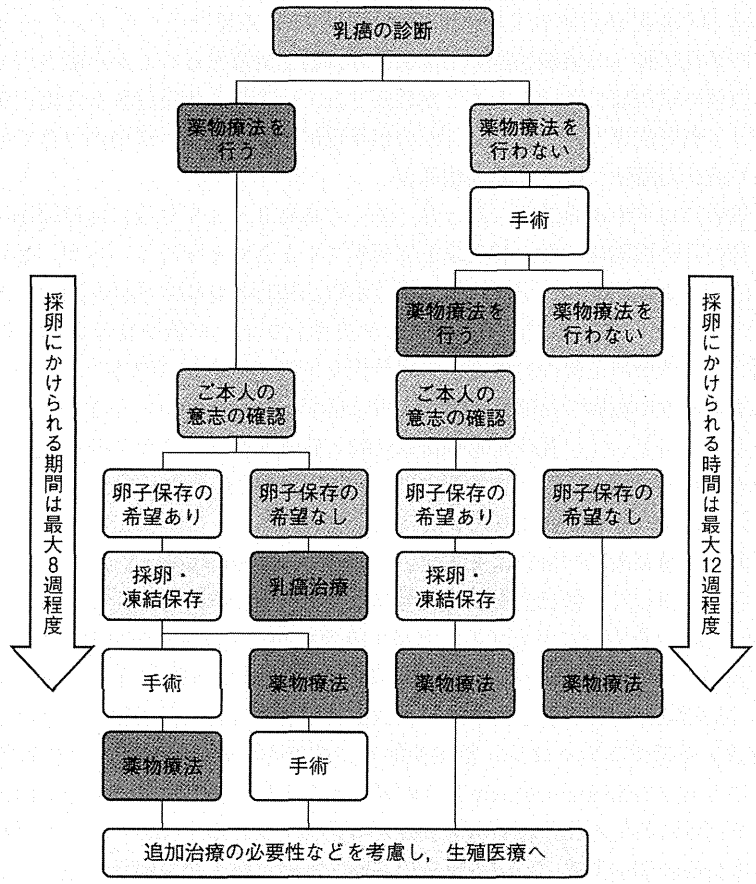


**図4　乳癌治療と生殖医療の流れ**

られる．アメリカではすでにこれらのデータベース構築に向け始動しており，妊娠期乳癌については患者のネットワークが作られさまざまな情報提供が為されている[43~45]．国内でも妊娠・出産を希望する乳癌患者と癌治療医・生殖医療専門医に役立つツールを作成し発信していきたい．

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# Efficacy of goserelin plus anastrozole in premenopausal women with advanced or recurrent breast cancer refractory to an LH-RH analogue with tamoxifen: Results of the JMTO BC08-01 phase II trial

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**Abstract.** The aim of the present study was to assess the efficacy and tolerability of a luteinizing hormone-releasing hormone (LH-RH) analogue plus an aromatase inhibitor following failure to respond to standard LH-RH analogue plus tamoxifen (TAM) in premenopausal patients. Premenopausal women with estrogen receptor (ER)-positive and/or progesterone-receptor positive, advanced or recurrent breast cancer refractory to an LH-RH analogue plus TAM received goserelin (GOS) in conjunction with anastrozole (ANA). The primary endpoint was the objective response rate (ORR). Secondary endpoints included progression-free survival (PFS), overall survival (OS), clinical benefit rate (CBR) and safety. Between September 2008 and November 2010, 37 patients were enrolled. Thirty-five patients (94.6%) had ER-positive tumors, and 36 (97.3%) had human epidermal growth factor receptor (HER) 2-negative tumors. Thirty-six (97.3%) had measurable lesions and 1 (2.7%) had only bone metastasis. The ORR was 18.9% [95% confidence interval (CI), 8.0-35.2%], the CBR was 62.2% (95% CI, 44.8-77.5%) and the median PFS was 7.3 months. Eight patients had adverse drug reactions but none resulted in discontinuation of treatment. GOS plus ANA is a safe effective treatment for premenopausal women with hormone receptor-positive, recurrent or advanced breast cancer. The treatment may become viable treatment in the future, particularly when TAM is ineffective or contraindicated. Further studies and discussion are warranted.

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*Key words:* aromatase inhibitor, breast cancer, luteinizing hormone-releasing hormone analogue, premenopausal patient, tamoxifen

## Introduction

Approximately 70% of all cases of breast cancer are hormone receptor-positive. Endocrine therapy is generally used for adjuvant treatment and the management of recurrence in hormone-sensitive breast cancer. Ovarian suppression induced surgically or with a luteinizing-hormone-releasing hormone (LH-RH) analogue as a postoperative adjuvant therapy can prevent recurrence and prolong survival in premenopausal women with breast cancer. The effectiveness of these treatments is comparable to that of chemotherapy (1,2). In premenopausal women, estrogen is synthesized primarily by the ovaries, and high estrogen concentrations are maintained in the blood. After menopause, the decline in ovarian function is accompanied by a significant decrease in estrogen concentrations in the blood, although levels remain high enough to stimulate the proliferation of breast cancer cells. Estrogen in postmenopausal patients is largely produced in peripheral adipose tissue and in cancer cells, and the peripheral aromatase is not under gonadotropin regulation (3). Therefore, aromatase inhibitors are used as standard treatment in postmenopausal

women with breast cancer following the cessation of ovarian function. Particularly in patients with recurrent or metastatic breast cancer, the major treatment objectives are to maintain or improve the quality of life (QOL) and to prolong survival. Treatment should therefore be initiated with endocrine therapy.

Endocrine therapy basically involves sequential administration of single agents. However, the combined use of an LH-RH analogue and tamoxifen (TAM) is superior to monotherapy (4) and is, therefore, the treatment of choice for premenopausal women with advanced or recurrent breast cancer. However, when the disease is resistant to combination therapy involving LH-RH analogue and TAM, alternative regimens for endocrine therapy are currently unavailable, with the exception of synthetic progesterone agents (medroxyprogesterone acetate). A number of patients must therefore receive chemotherapy. Consequently, the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines recommend that premenopausal women with advanced or recurrent breast cancer undergo ovarian ablation or suppression and then receive treatment similar to that recommended for postmenopausal women. The above mentioned guidelines recommend that premenopausal breast cancer patients undergo a combination treatment that includes an LH-RH analogue and an aromatase inhibitor. However, few studies support this treatment regime for premenopausal patients. Forward *et al* (5) studied goserelin (GOS) plus anastrozole (ANA) as a second-line endocrine therapy in 16 premenopausal women with advanced breast cancer who had previously received an LH-RH analogue plus TAM. After 6 months of treatment, 1 patient had partial response (PR), 9 had stable disease (SD) and 2 had a biochemical response. The clinical benefit rate was 75%. Serum estradiol levels were measured during treatment. Introduction of GOS and TAM reduced mean estradiol levels by approximately 89%. Substitution of TAM with ANA further decreased estradiol levels by 76%. This represents a marked decrease compared with the level during treatment using GOS and TAM.

These results suggest that combination therapy with an LH-RH analogue and an aromatase inhibitor is a viable treatment option for premenopausal women with breast cancer. To confirm this hypothesis, we studied the response rate to an LH-RH analogue plus ANA in women who failed to respond to an LH-RH analogue plus TAM. Progression-free survival (PFS), overall survival (OS), clinical benefit rate (CBR) and safety were also assessed.

## Patients and methods

*Study design.* This open-label, single-arm, multi-center, phase II study (registration no. UMIN000001217) was conducted to assess the efficacy and safety profile of an LH-RH analogue and an aromatase inhibitor combination therapy in patients with TAM-refractory, ER-positive, premenopausal metastatic breast cancer in Japan between September 2008 and February 2012. The following treatment was initiated within 4 weeks after enrollment. Anastrozole (Arimidex) 1-mg tablets were administered orally once daily. A 3.6-mg depot of GOS acetate (Zoladex) was injected subcutaneously into the lower abdomen once every 4 weeks (28 days). Treatment was continued until the development of progressive disease (PD) or unacceptable adverse events.

This study was conducted in accordance with the Declaration of Helsinki, and the Ethical Guidelines for Clinical Studies, July 30, 2003 (Amended December 28, 2004) by the Ministry of Health, Labor and Welfare, Japan. This protocol was approved by JMTO (The Japan-Multinational Trial Organization) Ethics Committee in February 2008 and was also approved by the Ethics Committee of each institution. The local assessment [complete response (CR), PR or prolonged SD of ≥24 weeks] was confirmed independently by two radiologists.

*Eligible patients.* Eligible patients had to meet all of the following inclusion criteria at study entry: premenopausal women 20-55 years of age (at enrollment); a confirmed diagnosis of metastatic or recurrent breast cancer; measurable lesions [according to Response Evaluation Criteria in Solid Tumors (RECIST)] or assessable bone lesions; refractoriness to previous treatment with an LH-RH analogue plus TAM; compliance with one of the following four conditions: i) recurrence while receiving postoperative therapy with an LH-RH analogue plus TAM; ii) recurrence within 1 year after the completion of at least 2 years of postoperative treatment with an LH-RH analogue plus TAM; iii) recurrence while receiving postoperative treatment with TAM alone after at least 2 years of treatment with an LH-RH analogue plus TAM or recurrence within 1 year after the completion of treatment with TAM, or iv) progressive disease while receiving combination therapy with an LH-RH analogue plus TAM for the management of advanced or recurrent breast cancer; estrogen receptor (ER)- and/or progesterone receptor (PgR)-positive breast cancer (positivity rate ≥10% on immunohistochemical analysis), an Eastern Cooperative Oncology Group performance status of 0 or 1; in patients who were receiving bisphosphonates, measurable lesions in sites other than the bone able to be followed up for antitumor response; with no serious complications; and written informed consent to participate in the study, received directly from the patient.

Patients were excluded from the study if they met any of the following criteria: i) a history of allergy to the study drug or concurrently used drugs; ii) treatment with other antitumor agents after prior therapy (LH-RH analogue plus TAM or LH-RH analogue plus TAM→TAM); iii) continuous treatment with systemic corticosteroids (orally or intravenously); iv) advanced cancer in other organs <5 years after treatment; v) a history of thrombosis, such as deep vein thrombosis or cerebral infarction; vi) a history of serious cardiac disease, such as myocardial infarction, valvular disease, or heart failure; vii) hormone-replacement therapy for climacteric symptoms received for ≤4 weeks at the time of enrollment; viii) women who were pregnant, breast feeding, or possibly (planning to be) pregnant; ix) treatment with antineoplastic agents other than an LH-RH analogue plus ANA, bisphosphonates, or radiotherapy of target lesions scheduled to be received after the start of the study; and x) patients considered unsuitable for the study by the investigator.

*Study variables.* The variables investigated included age, body-mass index, tumor diameter of the primary lesion, lymph-node metastasis, ER, PgR, human epidermal growth factor receptor (HER) 2 status, sites of metastasis or recurrence, performance

status at enrollment (according to the Eastern Cooperative Oncology Group), the presence or absence of postoperative radiotherapy, and the presence or absence of chemotherapy. Immunohistochemical staining was used to evaluate ER, PgR and HER2. ER and PgR were judged to be positive if the percentage of positive cells was ≥10%. HER2-positivity was defined as 3+ by immunohistochemistry or HER2 amplification by fluorescent *in situ* hybridization (HER2/CEP17 >2.0).

*Endpoints*. The primary endpoint was the response rate. Tumor shrinkage was evaluated according to the RECIST version 1.0 (6), and response was categorized as CR, PR, SD or PD. Bone lesions are generally considered non-target lesions as they are unmeasurable. However, bone is a common site of metastasis from breast cancer, in which the rate of metastasis is as high as 70-80%. In the present study, bone metastases were considered target lesions for the evaluation of response only in patients who only had bone metastases. The response of bone lesions was evaluated according to the standards of the Japanese Breast Cancer Society (7). If lesions existed in sites other than bone, bone lesions were evaluated as non-target lesions.

Secondary endpoints were PFS, OS, CBR and safety. PFS was defined as the number of days from enrollment to an initial event (disease progression or mortality from any cause, whichever occurred first). CBR was defined as the percentage of patients who had a CR, PR or prolonged SD maintained for at least 24 weeks among all eligible subjects. Safety was evaluated according to the Common Terminology Criteria of Adverse Events (CTCAE), version 3.0 (8).

*Statistical analysis*. The design of this study was based on a binomial distribution with no planned interim analysis. Assuming a null hypothesis of a 6% ORR and an alternative hypothesis of a 20% ORR, with one-sided type I error = 0.025 and type II error = 0.2, the required sample size was calculated to be 33. The planned sample size was set at 35, with the consideration of ~5% of patients being ineligible.

Exact confidence intervals (95% CI) were calculated for CBR and ORR. PFS and OS were estimated by the Kaplan-Meier method. The incidence of grade 3 or 4 adverse events is shown according to type. If an adverse event of the same type and the same grade developed twice in the same patient, it was counted as one event. Statistical analysis was performed with SAS System Release 9.1.3 (SAS Institute Inc., Cary, NC, USA).

## Results

*Patient characteristics*. From September 2008 to November 2010, a total of 37 patients were enrolled in the study. The patients were followed up and outcomes were confirmed in February 2012. Table I shows the demographic characteristics of the 37 patients. The median age was 43.0 years (range, 33-53), and the median body-mass index was 21.6 kg/m$^2$ (range, 16.9-30.3). The median disease-free interval (DFI) was 58.0 months (range, 0.9-201.3) and 12 patients (42.9%) had longer DFI (>60 months). ER/PgR status was ER+/PgR+ in 27 patients (73.0%), ER+/PgR- in 8 (21.6%) and ER-/PgR+ in 2 (5.4%). HER2 was negative in 36 patients (97.6%). During prior treatment with an LH-RH analogue plus TAM, 26 patients (70.3%) had PD, and 6 (16.2%) had recurrence during postoperative adjuvant therapy; 5 patients (13.5%) had completed the previous course of adjuvant therapy. Previous treatment included radiotherapy in 13 patients (35.1%) and chemotherapy in 20 (54.1%).

Table I. Patient characteristics.

| Characteristics (n=37) | Median | Range |
|---|---|---|
| Age (years) | 43.0 | 33-53 |
| BMI (kg/m$^2$) | 21.6 | 16.9-30.3 |
| Disease-free interval (months; 28 recurrent cases) | 58.0 | 0.9-201.3 |

| Characteristics (n=37) | No. of patients | % |
|---|---|---|
| ER and PgR status | | |
| ER+ and PgR+ | 27 | 73.0 |
| ER+ and PgR- | 8 | 21.6 |
| ER- and PgR+ | 2 | 5.4 |
| HER2 status | | |
| Negative | 36 | 97.3 |
| Unknown | 1 | 2.7 |
| Description of previous treatment (LH-RHa + TAM) | | |
| Recurrence during postoperative therapy | 6 | 16.2 |
| Recurrence within 1 year after completing postoperative therapy | 1 | 2.7 |
| Recurrence during continued adjuvant therapy with TAM alone or within 1 year after completion | 4 | 10.8 |
| Disease progression during treatment for advanced or recurrent breast cancer | 26 | 70.3 |
| History of other previous treatments | | |
| Prior radiotherapy | 13 | 35.1 |
| Prior chemotherapy | 20 | 54.1 |
| Presence of metastatic sites (n=37) | | |
| No | 6 | 16.2 |
| Yes | 31 | 83.8 |
| Metastatic sites (n=31) | | |
| Breast | 2 | 6.5 |
| Skin | 2 | 6.5 |
| Lymph nodes | 12 | 38.7 |
| Bone | 14 | 45.2 |
| Lung | 9 | 29.0 |
| Pleura | 1 | 3.2 |
| Liver | 9 | 29.0 |
| Type of treated lesions (n=37) | | |
| Measurable disease | 15 | 40.5 |
| Measurable + bone | 21 | 56.8 |
| Bone only | 1 | 2.7 |

LH-RHa, luteinizing hormone-releasing hormone analogue; TAM, tamoxifen; HER2, human epidermal growth factor receptor 2; ER, estrogen receptor; PgR, progesterone receptor.

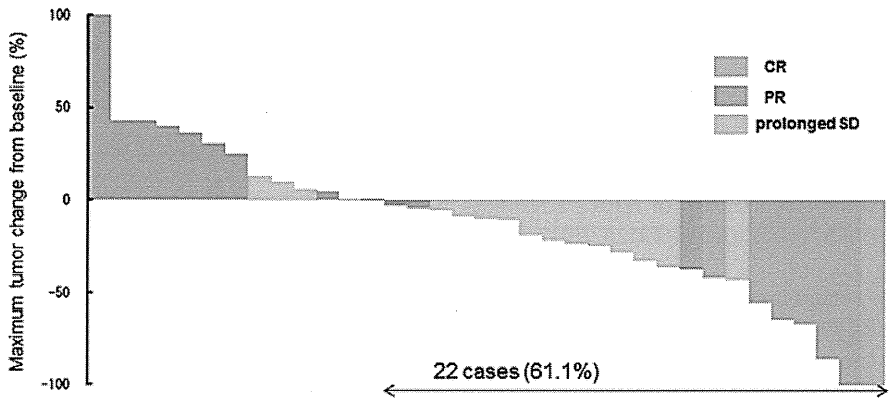


Figure 1. Waterfall plot of maximal change (%) in RECIST-evaluable tumor size from baseline. Thirty-six patients had measurable disease at baseline, and tumor shrinkage was found in 22 patients (61.1%). Of the patients with long-SD, 12 patients (75%) had tumor shrinkage. CR, complete response; PR, partial response; SD, stable disease.

Table II. Objective response rates and clinical benefit rates.

| Response | No. of patients | % | 95% CI |
|---|---|---|---|
| Complete response | 1 | 2.7 | |
| Partial response | 6 | 16.2 | |
| Objective response | 7 | 18.9 | 8.0-35.2 |
| Stable disease ≥24 weeks | 16 | 43.2 | |
| Clinical benefit | 23 | 62.2 | 44.8-77.5 |
| Stable disease <24 weeks | 2 | 5.4 | |
| Progressive disease | 11 | 29.7 | |
| Not evaluable[a] | 1 | 2.7 | |

[a]Response was not assessable in 1 patient who withdrew her informed consent as she wanted to receive a folk remedy. CI, confidence interval.

Thirty-one patients had distant metastases and 6 had locally advanced disease. The sites of metastasis were bone in 14 patients, lymph nodes in 12, liver in 9, lung in 9, contralateral breast in 2, distant skin in 2 and pleura in 1. Thirty-six patients (97.3%) had measurable disease, 21 (56.8%) of the patients also had bone lesions and 1 had only bone metastasis.

*Clinical effectiveness*. Clinical effectiveness is summarized in Table II. One patient (2.7%) had a CR, and 6 (16.2%) had PR for a response rate of 18.9% (95% CI, 8.0% to 35.2%; P=0.006 under the null hypothesis of a 6% ORR). Sixteen patients (43.2%) had prolonged SD. The CBR was thus 62.2% (23 patients, 95% CI, 44.8-77.5%). Eleven patients (29.7%) had PD. One patient with a response of not evaluable withdrew her informed consent as she wanted to receive a folk remedy. Fig. 1 shows a waterfall plot of maximal change (%) in RECIST-evaluable tumor size from baseline. Thirty-six patients had measurable disease at baseline, and tumor shrinkage was found in 22 patients (61.1%). Of the patients with prolonged SD, 12 patients (75%) had tumor shrinkage.

Regarding the previous treatment (LH-RH analogue + TAM) status, the ORR of the patients was as follows; 16.7% (1/6) in the recurrence group during postoperative therapy, none (0/1) in the recurrence group within 1 year after completing postoperative therapy, none (0/4) in the recurrence group during continued adjuvant therapy with TAM alone or within 1 year after completion, and 23.1% (6/26) in the disease progression group during treatment for advanced or recurrent breast cancer.

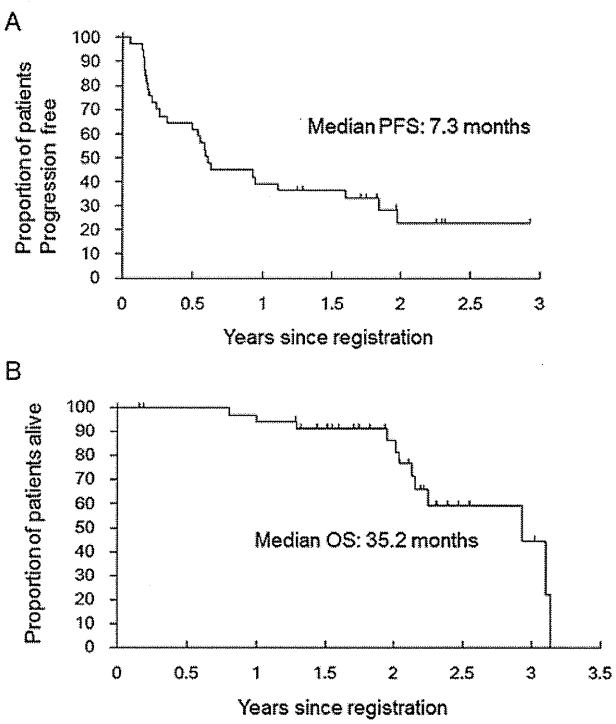


Figure 2. (A) Progression-free survival (PFS) and (B) overall survival (OS) since registration of the 37 enrolled patients. The median PFS and OS were 7.3 and 35.2 months, respectively. New lesions developed in 12 patients, 9 had progression of non-target lesions and 1 had progression of target lesions. Breast cancer was responsible for the 12 deaths.

*Patient outcomes*. Fig. 2 shows PFS and OS. The median PFS was 7.3 months. New lesions developed in 12 patients, 9 had progression of non-target lesions, and 16 had progression of target lesions. The median OS was 35.2 months. Breast cancer was responsible for the 12 deaths.

Table III. Adverse events and adverse drug reactions.

| | Adverse events | | Adverse drug reactions | |
|---|---|---|---|---|
| Event | Grade 1 | Grade 2 | Grade 1 | Grade 2 |
| Hot flashes | 9 | | 3 | |
| Joint pain | 5 | 1 | 1 | 1 |
| Sweating | 7 | | 1 | |
| Laboratory abnormalities[a] | 3 | | 3 | |
| Insomnia | 3 | | 1 | |
| Pain (limbs) | 3 | | | |
| Arthritis (non-septic) | 2 | | | |
| Fracture[b] | | 1 | | |
| Precordial pain | 1 | | 1 | |
| Fatigue | 1 | | 1 | |
| Nausea | 1 | | 1 | |

[a]Laboratory abnormalities: abnormal RBC, total cholesterol and ALT values occurred in 1 patient each. [b]Fracture: a fissured fracture occurred after stumbling. There were no grade 3 or 4 adverse events.

*Adverse events*. Adverse events are shown in Table III. Most adverse events were grade 1. One patient had grade 2 arthralgia and 1 had a grade 2 bone fracture. Adverse drug reactions for which a causal relationship to treatment could not be ruled out are shown. A total of 13 events occurred in 8 patients. With the exception of the grade 2 arthralgia (1 patient), all other events were grade 1. Treatment was not discontinued due to adverse events in any patient. There were no safety issues according to the IDMC.

## Discussion

Few confirmatory studies have been performed with aromatase inhibitors in combination with luteinizing hormone-releasing hormone (LH-RH) analogue in premenopausal women with recurrent or advanced breast cancer. Therefore, we studied the clinical effectiveness of creating a goserelin (GOS) and anastrozole (ANA) combination therapy for breast cancer patients who failed to respond to an LH-RH analogue plus tamoxifen (TAM). The response rate was 18.9%, with a clinical benefit rate (CBR) of 62.2%, a median progression-free survival (PFS) of 7.3 months, and a median overall survival (OS) of 35.2 months. On disease progression, second-line treatment options include other types of endocrine therapy for estrogen receptor (ER)-positive breast cancer. Moreover, hormone resistance includes primary (*de novo*) and secondary (acquired) resistance, and the mechanism of resistance between them may differ. It was reported (9) that the patients with secondary resistance responded to the second-line treatment. According to the previous treatment status (LHRH analogue + TAM), the objective response rate (ORR) in the patients (possibly primary resistance) with recurrence during adjuvant therapy or within 1 year after completion was low [total, 9.1% (1/11)]. On the other hand, the ORR was high (23.8%, 6/26) in the patients with disease progression during treatment for advanced or recurrent breast cancer. Although there were several cases with longer disease-free interval (DFI) (possibly secondary resistance), it was difficult to distinguish between primary and secondary hormone resistance in the present study.

Aromatase inhibitors have been shown to increase gonadotropin secretion and to activate ovarian function in premenopausal women (10,11). By contrast, LH-RH analogues inhibit ovarian function and create a postmenopausal hormone environment, facilitating a response to treatment with an aromatase inhibitor. The above mentioned treatment suggests that the combination of aromatase inhibitors with an LH-RH analogue could obtain a complete estrogen blockade by suppressing the ovarian function and the synthesis of peripheral estrogen. In addition, this treatment may produce substantial antitumor activity in premenopausal women (8). Forward *et al* (5) and Carlson *et al* (12) clearly described this hormonal environment.

A meta-analysis comparing an LH-RH analogue alone with an LH-RH analogue plus TAM in premenopausal women with advanced breast cancer showed that the ORR was 29.7 and 38.8%, the median PFS was 5.4 and 8.7 months, and the median OS was 2.5 and 2.9 years, respectively. Outcomes were significantly improved in patients who also received TAM (13). On the basis of these results, an LH-RH analogue plus TAM is currently the standard therapy for premenopausal breast cancer. Regarding the treatment of postmenopausal women with recurrent breast cancer, aromatase inhibitors can be considered a standard endocrine therapy as first-line and second-line treatments (14-18). Aromatase inhibitors appear to be a viable treatment option in combination with an LH-RH analogue given to induce a postmenopausal hormonal environment for premenopausal women with breast cancer.

In the present study, an LH-RH analogue plus an aromatase inhibitor were administered to premenopausal women who failed to respond to an LH-RH analogue plus TAM. In a separate study of first-line treatment with an LH-RH analogue and an aromatase inhibitor in 32 premenopausal women with metastatic breast cancer (12), 1 patient (3.1%) had complete response (CR) and 11 (34.4%) had partial response (PR). All patients had a clinical benefit rate (CBR) of 71.9% and a time to progression of 8.3 months (range, 2.1-63). These results were better than those obtained in our study. The majority of the patients were hormone-naïve (12), while all patients in our study were treated with an LH-RH analogue plus TAM, including the patients who developed recurrence within 1 year after the completion of postoperative treatment with an LH-RH analogue plus TAM. This data supports the recommendations of the NCCN which indicates that the patients who received prior endocrine therapy within 1 year are potential candidates for this treatment.

With regard to the second-line treatment, a retrospective study of GOS plus letrozole (n =16) in premenopausal women with advanced breast cancer (19) reported an ORR of 12.5% (1/16) and a CBR of 56.3% (9/16), which is similar to the results obtained in our study. Furthermore, our prospective study demonstrates the benefits of the GOS plus ANA treatment in premenopausal women refractory to an LH-RH analogue with TAM.

The Austrian Breast and Colorectal Cancer Study Group trial 12 (ABCSG-12) compared an LH-RH analogue plus TAM with an LH-RH analogue plus an aromatase inhibitor as an adjuvant therapy in premenopausal women with endocrine-responsive breast cancer (20). They found that there was no significant difference between the two endocrine therapy groups and that further observation is necessary. In a retrospective study evaluating the effectiveness of letrozole plus an LH-RH analogue administered concurrently with preoperative chemotherapy and as an adjuvant treatment in premenopausal women with locally advanced ER-positive breast cancer (21), the pathological CR rate, decrease in Ki-67 level, and a higher 5-year disease-free survival rate were significantly improved compared to those in a control group of similar patients who received preoperative chemotherapy followed by TAM plus and an LH-RH analogue after surgery.

The STAGE study by Masuda *et al* (22) was a randomized, double-blind trial of ANA vs. TAM in patients receiving GOS for premenopausal breast cancer in the neoadjuvant setting. The study showed that ANA demonstrated a superior benefit-risk profile compared with TAM as a neoadjuvant treatment in premenopausal women with ER+ breast cancer receiving GOS.

Only 1 patient in our study had a grade 2 adverse drug reaction (arthralgia) and the rest had grade 1 events. No patient discontinued treatment due to adverse events, which were relatively low and were considered symptoms associated with ANA in postmenopausal women. Previous studies have also reported that GOS plus ANA is safe, with no serious adverse events (12).

In conclusion, our results suggest that combination therapy with GOS and ANA is a safe, highly effective, viable treatment for premenopausal women with hormone-sensitive, recurrent or advanced breast cancer. We consider that GOS plus ANA will be recognized as a standard treatment for premenopausal ER-positive recurrent breast cancer, particularly when TAM is contraindicated or ineffective. Further studies and discussion are required to support these results.

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# An overview of the Japan Breast Cancer Research Group (JBCRG) activities

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**Abstract** The purpose of this article is to describe the current status and future perspectives of the Japan Breast Cancer Research Group (JBCRG). The JBCRG was organized in 2002, with the following purpose: to plan and promote clinical trials and basic research in breast cancer domestically and multilaterally; to conduct research and surveys on domestic and foreign information on medical care for breast cancer and to diffuse and highlight such information; to improve and promote clinical technologies for breast cancer; to act as an intermediary to liaise and strengthen alliances with affiliated organizations; and, to contribute to the public welfare by improving outcomes in breast cancer. The clinical trials are led by doctors/investigators in the JBCRG. And the purpose is to establish standard treatment for patients and provide substantial evidence. The JBCRG implements international collaboration in some researches/studies. As of January 2012, fourteen trials have been closed and nine are open to recruitment.

**Keywords** Clinical trials · Clinical research · Preoperative systemic therapy · Breast cancer

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## Introduction

The incidence of breast cancer in Japan has increased yearly; thus, more attention has been given to breast cancer treatment, among all cancers. In order to save as many breast cancer patients as possible, and to improve their quality of life (QOL), new diagnostic methods, treatments, and prophylaxes for breast cancer should be developed.

The JBCRG shall carry out the following, to serve the aforementioned purpose:

1. Basic and clinical research
2. Collection, analysis, and publication of information
3. Mutual exchange of information
4. Ordinary/extraordinary general meetings
5. Any other affairs required to accomplish the purpose of the JBCRG

The JBCRG has conducted mainly phase II trials to give answers to clinical questions, and now is planning to start phase III ones to achieve clinical approval of new standard therapies. The JBCRG is soliciting donations from organizations and individuals who wish to support its activities. The JBCRG usually manages data quality by central monitoring at data centers including the JBCRG Data Center, which is located in the Kyoto Technoscience Center, Kyoto; however, in some studies such as the SOLE trial, the JBCRG conducted site visits for source document verification.

As of January 2012, 243 doctors from 154 institutes are registered as JBCRG members who are specialists from the breast cancer treating hospitals around Japan. Also, the JBCRG is a member of the Breast International Group (BIG), which is an international breast cancer research group. Tables 1 and 2 summarize the closed and ongoing clinical trials, respectively.

**Table 1** JBCRG trials closed/in follow-up

| Trial | Design | No. of pts | Primary endpoints | Regimen | Enrollment start date |
|---|---|---|---|---|---|
| Neoadjuvant setting | | | | | |
| 1 | Phase II | 202 | Clinical response, safety | FEC100 q3w×4 → Doc75 q3w×4 | Jun 02 |
| 2 | Phase II | 31 | Clinical response, safety | FEC100 q3w×4 → Doc100 q3w×4 | Aug 04 |
| 2′ | Validation | 19 | Clinical response, histological effects, safety | FEC100 q3w×4 → Doc100 q3w×4 | Dec 05 |
| 3 | Phase II | 130 | Histological effects, safety | Doc75 q3w×4 → FEC100 q3w×4 | Oct 05 |
| 5 | Phase II | 33 | Response rates | Doc75 q3w×4 → letrozole 12 (−18) w | Sep 07 |
| 6 | Phase II | 40 | Response rates | Letrozole 12 (−18) w | Sep 07 |
| 7 | Phase II | 40 | Response rates | Letrozole + cyclophosphamide 24 w | Oct 07 |
| 10 | Randomized phase II | 180 | Pathological CR rate | (1) FEC×4 → TCH×4, (2) TCH×4 → FEC×4, (3) TCH×6 | Jun 09 |
| 13 | Phase II | 40 | Pathological CR rate | Metronomic PCX 4 → FEC×4 | Jan 10 |
| Postoperative setting | | | | | |
| 4 (CREATE-X) | Phase III | 900 | Disease-free survival | Any preoperative systemic therapy ± capecitabine | Feb 07 |
| SOLE with BIG | Phase III | 4,800 | Disease-free survival | Intermittent or continuous letrozole | Apr 10 |
| 8 ALTTO | Phase III | 140 | Disease-free survival | Lapatinib and/or trastuzumab | Jul 07 |
| Metastatic setting | | | | | |
| M01 | Phase I | 6 | MTD, DLT, RD | CPT11 + S1 | Jul 06 |
| M01 | Phase II | 37 | Response rates, clinical efficacy | CPT11 + S1 | Jul 06 |
| M02 | Phase II | 50 | Response rates | Letrozole | Nov 06 |
| Cohort study | | | | | |
| C01 | Cohort | 1,500 | Disease-free survival | Trastuzumab | Sep 07 |

Data correct as of 31 March 2012

*CR* complete response, *MTD* maximum tolerated dose, *DLT* dose limiting toxicity, *RD* recommended dose, *FEC* 5-fluorouracil + epirubicin + cyclophosphamide, *Doc* docetaxel, *TCH* docetaxel + cyclophosphamide + trastuzumab, *PCX* paclitaxel + cyclophosphamide + capecitabine

## Neoadjuvant pharmacotherapy

The first clinical trial conducted by the JBCRG was JBCRG-01, a phase II trial of preoperative systemic therapy (PST) using fluorouracil, epirubicin, and cyclophosphamide (FEC) followed by docetaxel (Doc) in patients with primary operable breast cancer [1–3]. Subsequently, JBCRG-02 study was conducted using FEC followed by Doc100 to investigate the safety and feasibility of 100 mg/m$^2$ Doc as PST. JBCRG-03 was a study to clarify the most effective sequence of FEC and Doc75 [4]. From the results of these studies, we defined new criteria of pathological response to PST, quasi pathological complete response (QpCR), total or near total disappearance of the invasive tumor in the removed breast. QpCR following preoperative chemotherapy predicts favorable disease-free survival (DFS). HER2 overexpression and clinical response to FEC predict QpCR [5, 6].

### *JBCRG-01*

JBCRG-01 was started in 2002 [1–3]. This multicenter phase II study examined the impact of pathological effect on survival after preoperative chemotherapy in Japanese women with early-stage breast cancer (ESBC). Prior to surgery, patients received four cycles of FEC (fluorouracil 500 mg/m$^2$, epirubicin 100 mg/m$^2$, cyclophosphamide 500 mg/m$^2$ q3w) followed by four cycles of docetaxel (75 mg/m$^2$ q3w). The primary endpoint was 3-year DFS stratified by the absence or presence of QpCR (absence of invasive tumor or only focal residual tumor cells). Secondary endpoints were predictors for QpCR, clinical response, breast conservation rate, and safety. Between June 2002 and June 2004, 202 women were enrolled. Among 191 assessable patients, 25 % achieved QpCR. With 40 months median follow-up, 3-year DFS was estimated at 91 % for all patients. The 3-year DFS for patients

**Table 2** JBCRG trials open to recruitment

| Trial | Design | No. of pts | Primary endpoints | Regimen | Enrollment start date |
|---|---|---|---|---|---|
| Neoadjuvant setting | | | | | |
| 9 | Randomized phase II | 195 | Histological response | TC×6, FEC×3 → TC×3,TC×3 → FEC×3 | Sep 09 |
| 11CPA | Phase II | 55 | Response rates | Letrozole ± low dose cyclophosphamide | Oct 10 |
| 11TC | Phase II | 60 | Clinical response | Exemestane 12w or exemestane 12w+TC×4 | Oct 10 |
| Postoperative setting | | | | | |
| 15 | Phase II | 30 | Pharmacokinetics | Toremifene | Mar 09 |
| SUPREMO with IBCSG | Phase III | 3,700 | Overall survival | Chest wall radiation | Jul 09 |
| Metastatic setting | | | | | |
| 12 | Phase II | 200 | CYP2D6 and pharmacokinetics | Tamoxifen and toremifene | Jan 10 |
| Cohort study | | | | | |
| C02 | Cohort | 100 | Progression-free survival | Trastuzumab | Jul 09 |

Data correct as of 31 March 2012

*TC* docetaxel + cyclophosphamide, *FEC* 5-fluorouracil + epirubicin + cyclophosphamide

with QpCR was 98 vs. 89 % for those without QpCR (hazard ratio 0.38 [95 % confidence interval 0.09–0.84], $P = 0.0134$). HER2 status and response to FEC were independent predictors of QpCR. The overall clinical response rate was 75 %; 85 % of patients achieved breast conservation. Grade 3/4 neutropenia was the most common adverse event, observed in 44 and 35 % of patients during FEC and docetaxel treatment, respectively. Treatment-related side effects were manageable; there were no treatment-related fatalities.

*JBCRG-02*

The JBCRG-02 study was conducted to evaluate the safety and clinical and histologic effects of primary systemic chemotherapy using FEC followed by docetaxel in primary breast cancer. The primary endpoints were safety and clinical and histologic effects. Secondary endpoints were breast-conserving rate and DFS. Fluorouracil 500 mg/m$^2$, epirubicin 100 mg/m$^2$, and cyclophosphamide 500 mg/m$^2$, q3w ×4 cycles, were followed by docetaxel 100 mg/m$^2$, q3w ×4 cycles, as primary systemic chemotherapy. Among patients receiving this regimen, 19.5 % experienced a pathological complete response and 9.7 % had a near pathological complete response, resulting in a QpCR of 29.2 %.

*JBCRG-03*

JBCRG-03 was a multicenter, open-label, single-arm, phase II study assessing the efficacy of a neoadjuvant chemotherapy with docetaxel (75 mg/m$^2$ q3w) followed by 5-fluorouracil 500 mg/m$^2$, epirubicin 100 mg/m$^2$, and cyclophosphamide 500 mg/m$^2$ q3w in patients with ESBC [4]. The primary endpoint was the pathological complete response (pCR) rate defined for the breast alone, assessed by a central review committee. Secondary endpoints included clinical response and safety. Of the 132 patients assessable for pathologic response, 23 % experienced a pCR and 6 % had a near pathological complete response (few remaining cancer cells), resulting in a QpCR of 29 %. Clinical response rate following the initial docetaxel regimen was 64 %. The overall clinical response rate was 79 %. Breast-conserving surgery was performed in 79 % of patients. More patients with triple-negative disease experienced a pCR (14/29, 48 %) versus those with other molecular subtypes. The safety profile was acceptable.

Oncotype DX

The 21-gene signature has been intensively studied and incorporated into major guidelines for treatment decision in early breast cancer. However, it remains to be examined whether this system is applicable to Asian populations.

*Retrospective analysis*

Toi et al. [7] were the first report to show that the 21-gene signature has value in providing prognostic information in Asian populations with estrogen receptor (ER)-positive, lymph node (LN)-negative breast cancer. A total of 325 tumor tissues were collected from ER-positive primary breast cancer patients who had undergone surgery and were

treated with tamoxifen between 1992 and 1998. The tissues were analyzed for the 21-gene signature, and the patients were classified into groups of low, intermediate, or high risk on the basis of the recurrence score. A total of 280 patients were eligible, with adequate reverse transcription polymerase chain reaction profiles for the recurrence score. Of those, 200 and 80 patients had LN-negative and LN-positive disease, respectively. The proportions of LN-negative patients categorized as being at low, intermediate, or high risk were 48, 20, and 33 %, respectively. In LN-negative patients, the Kaplan–Meier estimates of the distant recurrence rate at 10 years were 3.3 % (95 % CI 1.1–10.0 %), 0 %, and 24.8 % (95 % CI 15.7–37.8 %) for those in the low-risk, intermediate-risk, and high-risk groups, respectively. The risk of distant recurrence in the low-risk group was significantly lower than that in the high-risk group when the entire Kaplan–Meier plots were compared ($P < 0.001$, log-rank test). There was a significant difference for overall survival between the low-risk and the high-risk groups ($P = 0.008$, log-rank test).

Economic evaluation

*JBCRG-TR03*

This study evaluates the cost-effectiveness of two scenarios designed to include the assay into Japan's social health insurance benefit package: one for LN−, ER+, ESBC and another for LN±, ER+, ESBC [8]. An economic decision tree and Markov model under Japan's health system from the societal perspective is constructed with new evidence from the Japanese validation study. Incremental cost-effectiveness ratios are estimated as ¥384,828 (US$3,848) per quality-adjusted life year (QALY) for the LN− scenario and ¥568,533 (US$5,685) per QALY for the LN± scenario. Both estimates are not more than the suggested social willingness-to-pay for one QALY gain from an innovative medical intervention in Japan, ¥5,000,000/QALY (US$50,000/QALY). Sensitivity analyses show that this result is plausibly robust, because the incremental cost effectiveness ratios (ICERs) do not exceed the threshold despite various changes of assumptions made and values employed. Therefore, the inclusion of the assay in Japan's social health insurance benefit package for not only LN− diseases but also LN+ diseases is cost-effective. Such a decision can be justifiable as an efficient use of finite resources for health care.

Toxicity

Steroids and H(2) blockers are commonly used as supportive care for taxane-containing chemotherapy, but they also affect docetaxel's primary metabolizer, cytochrome P(450) 3A4. Kawaguchi et al. [9] performed a retrospective observational study to better understand the effects of these compounds on docetaxel-induced skin toxicities, specifically hand-foot syndrome (HFS) and facial erythema (FE), a relationship that is currently poorly understood. Member institutions of the JBCRG were invited to complete a questionnaire on the occurrence of grade 2 or higher HFS and FE among patients treated between April 2007 and March 2008 with docetaxel as an adjuvant or neoadjuvant chemotherapeutic treatment for breast cancer. We obtained data for 993 patients from 20 institutions. Twenty percent received H(2) blockers, and all patients received dexamethasone. Univariate and multivariate analyses revealed that H(2) blockers are associated with a significantly higher incidence of both HFS and FE. The incidence of FE was significantly higher for the docetaxel + cyclophosphamide (TC) regimen than for non-TC regimens combined. Dexamethasone usage did not affect the incidence of either HFS or FE. In conclusion, the use of H(2) blockers as premedication in breast cancer patients receiving docetaxel significantly increases the risk of both HFS and FE.

International study

The JBCRG is a member of the international breast cancer research group BIG. The JBCRG has joined in with several international clinical studies.

*JBCRG-04 (CREATE-X)*

This study aims to investigate the efficacy and safety of capecitabine, as a postoperative adjuvant chemotherapy, for breast cancer patients who were pathologically demonstrated to have residual cancer cells after the preoperative chemotherapy. In addition, the cost-effectiveness of capecitabine is to be investigated. The primary objective is DFS and secondary ones are overall survival, safety, and cost-effectiveness. Eligible patients had stage I-IIIB at the first diagnosis (curable breast cancer) and were non-pCR after preoperative chemotherapy including at least two cycles anthracycline agents; that is, they were confirmed pathologically by surgical and/or histological tests to have residual cancer cells. The patients had also been confirmed to be HER2 negative.

*JBCRG-08 (ALTTO)*

JBCRG-08 was a randomized, multicenter, open-label, phase III study of adjuvant lapatinib, trastuzumab, their sequence, and their combination in patients with HER2/ErbB2-positive primary breast cancer (BIG 2-06/N063D/EGF 106708.). The objective of this study was to compare DFS in patients with HER2 overexpressing and/or amplified

breast cancer randomized to trastuzumab for 1 year versus lapatinib for 1 year versus trastuzumab (12 weeks) followed by a 6-week treatment-free interval followed by lapatinib (34 weeks) versus trastuzumab in combination with lapatinib for 1 year. Endpoints were DFS, overall survival (OS), time to recurrence (TTR), time to distant recurrence (TTDR), safety and tolerability, cumulative incidence of brain metastases as the first site of breast cancer recurrence, presence or absence of cMyc gene amplification, expression levels of PTEN, and presence or absence of p95 HER2 domain. Trial periods were between July 2007 and February 2011 (registration, 2 years; follow-up study, 5 years). Target sample size was 140 from 15 institutions.

*SOLE trial*

SOLE trial is a phase III trial evaluating the role of continuous letrozole versus intermittent letrozole following 4–6 years of prior adjuvant endocrine therapy for postmenopausal women with hormone receptor-positive, node-positive ESBC. The JBCRG is collaborating with the International Breast Cancer Study Group (IBCSG) on this trial. A total of 4,800 patients are expected to be enrolled in this study. The primary endpoint is DFS, and secondary ones are OS, distant DFS, breast cancer-free interval, sites of first failure, second (non-breast) malignancies, deaths without prior cancer events, and adverse events.

*SUPREMO trial*

The SUPREMO trial is a randomized phase III trial assessing the role of chest wall irradiation in women with intermediate-risk breast cancer following mastectomy conducted by BIG. Postoperative radiotherapy is routinely given to patients at higher risk of recurrence with 4 or more LNs or large tumor(s). In patients with less than 4 LNs under the armpit involved by cancer or with no LNs involved but other features of the cancer that increase the risk of recurrence, it is not clear whether postoperative radiotherapy is needed. Eligibility criteria are a postoperative breast cancer patient who has had a mastectomy, and who has an intermediate risk of the cancer returning. An intermediate risk is diagnosed when there are less than 4 LNs under the armpit involved by cancer or there are no LNs involved, but there are other features of the cancer that mean it is more likely to come back. The trial will involve 1,600 women.

## Conclusion

The JBCRG was founded in order to perform good-quality multicenter studies, and related clinical trials in close liaison with research institutions in other countries and regions, as well as in Japan. The JBCRG has performed a variety of studies, including primary pharmacotherapy, pharmacotherapy for recurrent breast cancer, clinical trials on postoperative pharmacotherapy, prediction of prognosis in hormone receptor-positive breast cancer, and prediction of the effect of chemotherapeutic drugs. The JBCRG has reported a number of outcomes to academic societies and in journals, and has obtained a good reputation. The incidence of breast cancer in Japan has increased yearly; thus, more attention has been given to breast cancer treatment, among all cancers. In order to save as many breast cancer patients as possible, and to improve their QOL, we will develop new diagnostic methods, treatments, and prophylaxes for breast cancer.



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ORIGINAL ARTICLE

# Physicians' knowledge, attitude, and behavior regarding fertility issues for young breast cancer patients: a national survey for breast care specialists

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**Abstract**
*Background* Fertility is one of the key aspects of quality of life for breast cancer patients of childbearing age. The objective of this study was to describe fertility-related practice for young breast cancer patients in Japan and to identify healthcare provider factors that contribute to physicians' behavior towards fertility preservation.
*Methods* A cross-sectional survey was developed in order for Japanese breast cancer specialists ($n = 843$) to self-evaluate their knowledge, attitude, and behavior regarding fertility preservation. Survey items included questions regarding knowledge of and attitude toward fertility issues in cancer patients, fertility-related practice, potential barriers for the discussion of fertility with patients, and responding physicians' socio-demographic background.
*Results* Four hundred and thirty-four (52%) breast oncologists responded to the survey. Female and younger oncologists (age less than 50 years) had significantly higher probability of referring patients to reproductive specialists. Physicians who had better knowledge score and positive attitudes toward fertility preservation were more likely to discuss potential fertility issues with cancer patients. This was significantly associated with consultation and referral to reproduction specialists when encountering fertility issues with cancer patients. Risk of recurrence, lack of collaborating reproductive specialists, and time constraints in the clinic were identified as major barriers to discussion of fertility preservation with breast cancer patients.
*Conclusion* Female and younger physicians as well as physicians working in a multidisciplinary environment had positive attitudes and behavior towards fertility preservation in breast cancer patients. The development of comprehensive and interdisciplinary programs for healthcare providers is necessary to meet the expectations and fertility needs of breast cancer patients.

**Keywords** Fertility preservation · Breast cancer · Survivorship

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## Introduction

With improvement of cancer prognosis, fertility has become one of the key aspects of quality of life for breast cancer patients of childbearing age. Distress about interrupted childbearing is likely to persist in long-term female cancer survivors [1]. The American Society of Clinical Oncology (ASCO) has developed guidance for oncologists regarding available fertility preservation methods and related issues [2]: oncologists should address the possibility of infertility with patients during their reproductive years and be prepared to discuss possible fertility preservation options or refer appropriate and interested patients to

reproductive specialists as early as possible during treatment planning.

However, previous studies have shown that only 23% of the patients younger than 40 years of age were informed of potential infertility after cancer treatment in a single institution in Japan and less than half of oncologists were following the ASCO guideline in the USA [3, 4]. The practice of oncologists regarding fertility preservation in cancer patients of reproductive age may depend on multiple factors: the patient's medical and psychosocial condition [5, 6], the patient's knowledge [7], and physicians' knowledge about fertility preservation [8].

We have previously analyzed the decision-making process for adjuvant treatment in young breast cancer patients of reproductive age [3]. Significantly less patients expressed interest in fertility when they had children or advanced disease. Less aggressive treatment (without chemotherapy) was recommended by oncologists for patients who voluntarily expressed an interest in preserving fertility [3]. Nearly one-third of the patients who expressed an interest in fertility selected a different adjuvant treatment from the primary recommendation of the oncologist because of their concern for preserving fertility, whereas the majority of patients who did not express an interest in preserving fertility followed the oncologists' primary recommendation [3].

The awareness and attitude of patients in the clinic might reflect the ability of healthcare providers to provide an environment in which patients could bring up fertility issues. The objectives of this study include describing fertility-related practice for breast cancer patients in a variety of clinical settings in Japan and identifying healthcare provider factors that contribute to physicians' behavior regarding fertility preservation in young breast cancer patients.

## Methods

### Selection of participant

A cross-sectional survey was developed in order for board-certified breast oncologists of the Japanese Breast Cancer Society (JBCS), who are the main physicians treating breast cancer patients in Japan, to self-evaluate their knowledge, perception, and behavior regarding fertility issues in young breast cancer patients.

### Measures

The survey consisted of 49 items including questions regarding knowledge of and attitudes towards fertility in cancer patients, practice behavior of fertility-related discussions with patients, potential barriers for these discussions, and demographic background of the practitioners (Table 1). Survey items were derived from existing literature and multidisciplinary discussion. Physicians were asked to evaluate their agreement with the statements using a five-grade system (1, strongly agree; 2, agree; 3, cannot decide; 4, disagree; 5, strongly disagree).

1. Knowledge about fertility issues in breast cancer patients

To evaluate the accuracy of knowledge about fertility issues in breast cancer patients, the statements were developed from the latest JBCS treatment guideline [5]. For statements A-1 and A-4, the respondents were considered to have more accurate knowledge when the score was lower. For statements A-2 and A-3, the respondents were considered to have more accurate knowledge when the score was higher. Then the sum of (5 − "score for A-1") + ("score for A-2") + ("score for A-3) + (5 − "score for A-4") was calculated. The respondents with a higher sum were considered to have more accurate overall knowledge. A-5 was not used to evaluate the accuracy of knowledge because of lack of definite evidence, but correlated with the use of LHRH agonist for fertility preservation.

2. Practice behavior for breast cancer patients of reproductive age

Practice behavior statements consisted of 13 items including statements used in the US oncologist survey with some modifications to adapt to Japanese practice setting. The statements "I discuss the impact of cancer treatment on future fertility with my patients", "I consult reproductive specialists with questions about fertility issues in my patients", and "I refer patients who have questions about fertility to reproductive specialists" were considered the most important behavior according to the ASCO guideline [2].

3. Potential barriers for discussing fertility issues with breast cancer patients

Among seven potential barriers asked in the questionnaire, four were similar to statements used in the US survey [4]. We put three additional statements (patients' voluntary expression of interest, existence of spouse/partner, and support from co-medical staff) that were created by findings from our previous study [2] and by considering Japanese culture. In addition, we asked the participant to describe the greatest difficulty in discussing fertility in an open question.

4. Attitude towards fertility preservation of cancer patients

Five statements were selected from the US survey [4]. Because the hereditary aspect of breast cancer was considered to be not genuinely linked with perception of

**Table 1** Questionnaire statements

| |
|---|
| A. Knowledge about fertility issues of breast cancer patients |
| 1. Total dose of alkylating agents are related to infertility |
| 2. Pregnancy after breast cancer increases risk of recurrence |
| 3. Pregnancy after chemotherapy increases risk of deformity of the child |
| 4. Pregnancy should be avoided during tamoxifen treatment |
| 5. Luteinizing hormone releasing hormone (LHRH) analogue reduces the risk of chemotherapy-induced amenorrhea |
| B. Practice behavior |
| 1. Patients voluntarily bring up the fertility issues in the clinic |
| 2. I discuss the impact of cancer treatment to future fertility with my patients |
| 3. I do not feel comfortable to discuss fertility issue with my patients |
| 4. I take into account the history of childbirth when I discuss fertility issue with my patient |
| 5. I take into account whether she has a spouse/partner when I discuss fertility issue with my patient |
| 6. I take into account economical status of the patient when I discuss fertility issue with my patient |
| 7. I discuss fertility issues with breast cancer patients with high risk of recurrence |
| 8. Patients talk to co-medical staff about their concern about fertility |
| 9. I ask co-medical staff if a patient has an interest in fertility |
| 10. I provide my patients with educational material about fertility preservation |
| 11. I use LHRH analogue to preserve fertility |
| 12. I consult a reproductive specialist with questions about fertility issues in my patients |
| 13. I refer patients who have questions about fertility to reproductive specialists |
| C. Barriers for discussing fertility issues |
| 1. The patient does not express their interest in fertility |
| 2. The patient has high risk of recurrence |
| 3. The patient has economic problems |
| 4. The patient does not have a spouse/partner |
| 5. There is no place/person to refer my patients to for fertility preservation |
| 6. Time constraints affect my ability to discuss fertility preservation |
| 7. There is no support from co-medical staff |
| 8. What is the greatest difficulty in discussing fertility issues with young breast cancer patients? |
| D. Attitude toward fertility preservation |
| 1. Patients with poor prognosis should not pursue fertility preservation |
| 2. Posthumous parenting is troublesome for bereaved family |
| 3. Losing mothers will negatively affect bereaved children |
| 4. I fear passing hereditary cancer to a biological child |
| 5. Treating cancer is more important than fertility preservation |
| E. Demographics and medical backgrounds |
| 1. What is your gender? |
| 2. What is your age? |
| 3. What is your religious background? |
| 4. When did you graduate from medical school? |
| 5. What is your specialty? |
| 6. Where is your primary practice located? |
| 7. What kind of institution do you practice in? |
| 8. Is your institution a community-base hospital for cancer care? |
| 9. How many physicians are in your practice setting including you? |
| 10. Are there any female physicians in your practice setting? |
| 11. Are there any medical oncologists in your practice setting? |
| 12. Are there any breast cancer specialized nurses in your practice setting? |
| 13. Are there any cancer-specialized pharmacists in your practice setting? |
| 14. Is there a genetic counseling clinic in your practice setting? |
| 15. In a typical week, how many breast cancer surgeries are performed in your practice setting? |
| 16. In a typical week, how many breast cancer patients under 40 years of age do you see? |
| 17. Do you have a spouse/partner? |
| 18. Do you have children? |
| 19. Do you have relatives or close friends who passed away leaving behind minor children? |

fertility preservation, the item was not included in our analysis. Participants were considered to be positive toward fertility preservation if the sum of scores was higher than 3. The sum of scores for statements from D-1 through D-5 was calculated and the respondents with higher total score were considered as physicians with a "positive attitude" towards fertility preservation.

5. Individual and institutional background

The items included physicians' gender, age, religious background, length of professional career, and specialty. We also asked for a description of the practicing institution: the number of breast surgeries, the number of young breast cancer patients, presence of female colleagues in the team, the presence of one or more medical oncologist(s), breast cancer certified clinical nurse specialist (CNS), and board-certified pharmacists in the institution.

## Procedures

The study was carried out according to the National Guideline for Epidemiological Studies. The names of study participants and the institutions of breast oncologists were obtained from the JBCS website. After confirmation of each physician's affiliation, anonymous paper surveys were sent out to all 843 breast oncologists by mail with a return